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Review

Animal models of cardiac arrhythmias[1]

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1. Introduction

When surveying the literature with the intention of evaluating to which extent studies on animal models have contributed to the understanding of arrhythmia mechanisms in patients and in devising therapeutic strategies, one is struck by the differences between supraventricular and ventricular arrhythmias. In general, in the field of supraventricular arrhythmias there has been a strong interaction between experimental and clinical studies and there can be no doubt that the various animal models have been instrumental in understanding the mechanisms of clinical arrhythmias and in establishing different forms of therapy. Clearly, an animal cannot be transformed into a human patient, but despite species differences and differences in arrhythmogenic factors in animal models and humans, the similarity between arrhythmia mechanisms in experimental models and patients far outweigh the differences.

This similarity is less evident when considering ventricular arrhythmias. There are several reasons for this. First, many ventricular arrhythmias, such as those induced by acute ischaemia, cannot be studied in human patients because they occur unpredictably in situations where electrophysiological changes may develop within minutes. Second, even when in patients acute ischaemia is the trigger for arrhythmias, many other factors may influence arrhythmogenesis, such as the presence of a healed infarct, hypertrophy, dilatation, electrolyte disturbances or heart failure. Third, many factors determine whether, and if so, how often ventricular arrhythmias occur in the setting of acute ischaemia and/or a chronic myocardial infarction, and in experimental models usually only a single factor is taken into account. Still, the knowledge of arrhythmogenic mechanisms derived from animal studies has greatly contributed to the development of diagnostic and therapeutic strategies.

2. Supraventricular arrhythmias

2.1. Re-entrant tachycardias in the presence of accessory atrioventricular pathways

The history of these arrhythmias is rather bizarre because animal studies provided the basic arrhythmia mechanisms long before the syndrome was clinically recognized, because from 1967 onwards clinical studies unravelled in great detail the electrophysiological characteristics in patients without the investigators being aware of the early animal studies, and because to our knowledge only one single dog had been studied that possessed an accessory atrioventricular pathway.

In 1913 Mines described an experiment on a ring-like preparation of a tortoise heart in which he was able to initiate circulating excitation by electrical stimulation. He made the historical prediction: ''I venture to suggest that a circulating excitation of this type may be responsible for some cases of paroxysmal tachycardia as observed clinically'' [1].

After reading Kent's report [2] in which a human heart was described with a muscular connection between the right atrium and the right ventricle, Mines wrote in 1914: ''I now repeat this suggestion in the light of the new histological demonstration by Stanley Kent that the muscular connection between auricles and ventricles is multiple. Suppose that for some reasons an impulse from the auricle reached the main A–V bundle but failed to reach this 'right lateral' connection. It is possible then that the ventricle would excite the ventricular end of this lateral connection,

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not finding it refractory as normally it would at such a time. The wave spreading then to the auricle might be expected to circulate around the path indicated'' [3]. This was written 16 years before Wolff, Parkinson and White described the clinical syndrome that now bears their name [4], 18 years before Holzmann and Scherf ascribed the abnormal ECG in these patients to pre-excitation of the ventricles via an accessory atrioventricular bundle [5], and 53 years before the first studies in patients employing intraoperative mapping and programmed stimulation proved Mines' predictions to be correct [6–8]. At present, all the electrophysiological characteristics of accessory atrioventricular connections and their role in causing re-entrant tachycardias have been obtained in studies on human patients (for review see Wellens [9]) and only one study described pre-excitation in a dog [10]. In this study, which also described two patients, the important observation was made that atrial fibrillation induced in the dog, caused ventricular fibrillation as well because the accessory pathway had a short refractory period and conducted many impulses, which otherwise would have been blocked in the AV node. Still, at present there is certainly no need for an animal model of accessory atrioventricular pathways.

2.2. Atrioventricular nodal re-entrant tachycardia

The history of this arrhythmia is very different from that of the arrhythmias caused by accessory AV connections. Although it was again Mines [1,2] who formulated the basic mechanisms, clinical studies quickly followed and throughout this century there has been an intensive interaction between experimental and clinical studies (for review see [11] and [12]). For example, the first study employing programmed stimulation in patients to unravel the arrhythmia mechanisms and to treat the condition by pacemaker implantation by Coumel and co-workers in 1967 [13] quoted the early studies of Mines [1,2]. Also, the pioneering clinical studies of the 1980s allowing successful surgical treatment [14,15] or catheter ablation [16–18] of the arrhythmia, all quoted the microelectrode studies of the 1960s and 1970s on isolated rabbit heart preparations that provided insight into arrhythmia mechanisms on a cellular basis [19–22].

Today, we are confronted with a rather paradoxical situation: the history indicates a happy union between knowledge gathered by both experimental and clinical studies, the former preceding the latter, which finally resulted in the very successful treatment by radiofrequency catheter ablation [23–25]. Despite this success, there are still many uncertainties about the exact location of the re-entrant pathway and about the electrophysiological and structural properties of the two AV nodal pathways ('slow' and 'fast') that are thought to form the basis for AV nodal re-entry. The animal model most often used, the isolated superfused rabbit heart preparation, differs from the heart of patients suffering from AV nodal re-entrant tachycardia. It is extremely rare to induce sustained AV nodal re-entry in this preparation, but it is not uncommon to induce single echo beats by premature stimulation of the atrial or ventricular tissue [19–22,26–29].

In open-chested anaesthetized dogs, only one 'case report' of sustained re-entrant AV nodal tachycardia has been published [30], and reproducibly induced sustained tachycardia became only possible after a surgical procedure that blocked atrial impulses from the anterior input site to the AV node [31].

In patients with AV nodal re-entrant tachycardia, the hallmark for dual AV nodal pathways is the so-called 'jump' in the conduction curve [32]: when during regular pacing of the atria (A1) single premature atrial stimuli (A2) at progressively shorter coupling intervals are applied and the premature atrium–His bundle intervals (A2–H2) are plotted against the A1–A2 intervals, a sudden jump of 50 ms or more in the A2–H2 interval at a decrement in A1–A2 of 10 ms is taken as evidence for dual AV nodal pathways. At a critical coupling interval the 'fast' pathway is refractory, and conduction to the His bundle proceeds via the 'slow' pathway which has a shorter refractory period. In isolated rabbit heart preparations, such a jump has not been observed [33]. In the anaesthetized dog, a 'jump' was observed in one study only after left and right stellate ganglia had been removed [34]. In another study, no jump was found [35]. In yet another study, a jump in the A–V interval was ascribed to slow conduction or block in the peripheral Purkinje system rather than to functional dissociation of the AV node [36]. In isolated, perfused dog hearts, no jump occurs [37,38], although ventricular echoes could be reproducibly induced [39]. Whereas the clinical experience would suggest that atrial tissue is involved in the re-entrant circuit (for review see [12] and [40], but for a different point of view see [41]), mapping studies in the isolated, blood perfused dog heart showed that ventricular echoes are due to subatrial re-entry [39].

It would be desirable if an animal model could be found in which subtle manipulation of the autonomic nervous system (rather than a surgical procedure as described in [31]) would result in sustained AV nodal tachycardia being reproducibly induced. Answers could then be found to questions such as: Is the re-entrant circuit for single echo beats the same as that for sustained re-entry? Are there structurally different pathways? Are there multiple re-entrant circuits? What is the role of anisotropic conduction and of different input sites? In any case, there is no animal model for dual pathways as observed in humans.

2.3. Atrial flutter

Much of our knowledge about activation patterns during atrial flutter has been derived from animal studies, with the 1920 paper of Lewis, Feil and Stroud as the classical example [42]. Catheter electrode mapping in patients was

first performed by Puech and colleagues in 1956 [43] and due to advances in mapping techniques, recent studies in man [44] allowed comparison to data obtained in animal models [45]. On the basis of these studies, it is widely accepted that atrial flutter is due to re-entry.

There are a number of animal models in which atrial flutter was induced following the creation of anatomical lesions, by extending an anatomical obstacle such as the ostium of the vena cava superior by crushing the intercaval region [46,47], or by producing single lesions in the right atrium [48–50]. It is doubtful whether these models are representative of atrial flutter in patients.

Another type of flutter, depending on a Y-shaped surgical lesion in the right atrial free wall, causing the re-entrant circuit to consist of atrial tissue around the tricuspid ring [51] may have a clinical counterpart in postoperative flutter following surgical correction of congenital abnormalities [52].

The canine model developed by Boyden and Hoffman [53], in which right atrial enlargement was produced by banding of the pulmonary artery and by producing tricuspid regurgitation, may also have a clinical counterpart in patients with chronic obstructive pulmonary disease and tricuspid regurgitation. In those dogs, a functional zone of block and area of slow conduction set the stage for re-entry, rather than an anatomical obstacle. Functional re-entry is also observed in the sterile pericarditis model of canine atrial flutter, first described by Pagé et al. [54]. This model was developed because of the fact that following cardiac surgery in patients atrial flutter frequently occurs and this may be related to postoperative sterile pericarditis. Another form of functional re-entry causing atrial flutter was pharmacologically induced in isolated dog hearts by infusion of acetylcholine [55].

Despite subtle differences in the various forms of atrial flutter, one cannot but agree with Mary-Rabine and co-workers [56], that ''the history of atrial flutter clearly illustrates the bidirectional flow of information and the mutual stimulation between the basic and the clinical levels, leading both to a better understanding of the nature of the arrhythmia and to new therapeutic approaches''. It is now established that atrial flutter is due to a re-entrant wave in the right atrium, and that a zone of slow conduction located inferiorly and posteriorly in the right atrium is the target for catheter ablation.

2.4. Atrial fibrillation

Some crucial observations on the characteristics of atrial fibrillation were made long before technical developments allowed the simultaneous recording from multiple atrial sites, a prerequisite for documenting the complex activation sequence of fibrillation. Thus, in 1914 Garrey [57] without the help of electrophysiological or mechanical recordings established that a critical mass of tissue is needed to sustain fibrillation. He also suggested that fibrillation was due to '' . . . a series of ring-like circuits of shifting location and multiple complexity'' [58]. Some 70 years later, Allessie and co-workers could record simultaneously from 192 atrial sites in an isolated, Langendorff-perfused canine heart in which atrial fibrillation was induced by rapid atrial pacing during infusion of acetylcholine [59]. In essence, they confirmed Garrey's statement, which had been refined by Moe and Abildskov on the basis of both experimental observations and computer simulations that led to the formulation of the multiple wavelet hypothesis [60,61]. In the experiments of Allessie et al. [59] the presence of multiple independent wavelets was documented, and it was estimated that the critical number of wavelets in both atria necessary to maintain fibrillation was between 3 and 6. These results were largely confirmed by other studies in dog hearts [62] and also by mapping studies in patients with atrial fibrillation during open heart surgery [63,64].

In recent years, there has been a remarkable interaction between experimental and clinical studies, where important findings in animal models were soon thereafter confirmed in clinical studies. For example, repetitive induction of atrial fibrillation, or prolonged periods of rapid atrial pacing, in conscious goats gave rise to a marked shortening of the atrial refractory period, which persisted for a long time after restoration of sinus rhythm and predisposed to the reinduction of atrial fibrillation following cardioversion [65]. This was confirmed in patients [66–68], as was the finding originally made in canine hearts [70], that calcium blocking agents could attenuate this shortening of the refractory period [69]. Despite the great impact that the experimental studies have on clinical developments, including new strategies for therapy such as catheter ablation (see Ref. [67]), there are obvious differences between the atria of the experimental animals used and those of patients who spontaneously develop atrial fibrillation. In the experimental models, atrial fibrillation was induced in essentially normal hearts, either by shorter or longer periods of rapid pacing or repetitive induction of atrial fibrillation by burst pacing [65,70] or by pharmacologic means, such as infusion of acetylcholine [59,62]. Whilst this latter model may have its clinical counterpart in the relatively rare form of atrial fibrillation dependent on increased vagal tone [71], about 85% of patients with atrial fibrillation have an underlying structural cardiac abnormality or a metabolic disorder, often associated with atrial enlargement [72]. Acute atrial dilatation shortens the atrial refractory period and enhances the vulnerability to atrial fibrillation [73,74]. However, the effects of chronic stretch are most likely different from those of acute stretch, and would be more important in contributing to atrial fibrillation in patients. There is one study by Boyden et al. [75] in which atrial cellular electrophysiological characteristics of dogs with naturally occurring mitral valve disease leading to progressive atrial enlargement were studied. Some animals were followed for 5 years, before the electrophysiological study

was performed. Most dogs developed atrial arrhythmias, including atrial fibrillation. Surprisingly, the transmembrane potential characteristics of atrial cells of these animals were not significantly different from those of control animals, although some cells were found with resting membrane potentials below −60 mV that were inexcitable. This is in contrast to the findings of the studies mentioned earlier [65,66] and also in contrast to several studies in which cellular electrophysiological abnormalities have been documented in small, isolated atrial preparations obtained from fibrillating human atria [76–78]. In the study of Boyden et al. [75], massive interstitial fibrosis and cellular hypertrophy were found and the authors concluded that the morphological changes were much more important in causing atrial fibrillation than the slight, insignificant electrophysiological alterations they found. The increased size of the atria would permit the coexistence of many re-entrant circuits. The increase in connective tissue would promote inhomogeneous conduction, unidirectional block and re-entry [79]. Thus far, the emphasis in animal models of atrial fibrillation has been on electrophysiological characteristics in structurally normal hearts. To further diminish the gap between animal models and patients, the arrhythmogenic effects of structural changes deserve further study.

3. Ventricular arrhythmias

3.1. A hereditary model of sudden death

A colony of German shepherd dogs has been described with inherited ventricular arrhythmias and a predisposition for sudden death [80]. Sudden death most often occurs during sleep or at rest after exercise or excitement. The electrocardiogram does not show a prolonged QT interval, but frequently there is marked notching of the T wave. The arrhythmias are rapid polymorphic ventricular tachycardias, following long R–R intervals, and are most likely due to triggered activity induced by early afterdepolarizations in the Purkinje system [81]. In epicardial myocytes, the density of the transient outward current (I_{to}) was reduced, and the time constant of inactivation was reduced [82]. In addition, deficiencies in cardiac sympathetic denervations have been reported [83]. At first glance, this dog model bears a resemblance to the congenital long QT syndrome in which bradycardia induced polymorphic ventricular tachycardia and sudden death occur and in which genetic defects in ion channels regulating repolarization have been described [84,85]. However, the dogs have no prolonged QT interval and thus far, in patients with the long QT syndrome no deficiencies in I_{to} have been described [85]. Still, this animal model might have a clinical counterpart because patients have been described with polymorphous ventricular tachycardia (Torsade de pointes) who have a normal QT interval [86,87].

3.2. Ventricular arrhythmias caused by acute ischaemia

A great many experimental studies on this subject have been undertaken in the past decades. A rough distinction can be made into studies in which electrophysiological parameters relevant for understanding arrhythmia mechanisms were recorded (for Refs. see [88,89]), and those in which only the incidence of the lethal arrhythmia, ventricular fibrillation, was noted, usually in studies testing anti-arrhythmic drugs.

Validation of animal models for assessing the pathophysiology of acute myocardial ischaemia implicates consideration of the (1) diversity of cardiac diseases which involve acute ischaemia and (2) the variety of experimental models which have mostly been designed to mimic part of the complex events occurring in the human disease. Along this line of reasoning, mostly large animals (dogs, pigs, cats) are used to study ventricular arrhythmias, while mostly small animals (rats) are involved in studies about the changes in metabolic pathways consequent to ischaemia and reperfusion. In the former, multisite mapping of electrical activity is applied to the analysis of the mechanisms of ventricular tachycardia and fibrillation [90,91] whereas in small animals' hearts, which primarily serve the purpose to provide numerous and affordable samples for chemical analysis, arrhythmias are defined by ECG patterns and analyzed statistically on the basis of their incidence. Thus the main reason for selecting a certain animal species appears to be the suitability for the application of a specific technique, assuming that 'acute' human ischaemia/reperfusion can be compared with experimental ischaemia/reperfusion independently of the species selected. While this assumption might hold for the very global and basic changes in metabolism, it is doubtful that such a simplified concept is applicable to the study of arrhythmogenesis, as outlined below. According to a search in 'MEDLINE' a total of 1327 studies have been carried out between 1966 and 1996 for the assessment of ventricular fibrillation in the setting of myocardial ischaemia. 569 of these studies were carried out in dogs, 126 in pigs, 25 in guinea pigs, 51 in rabbits and 931 in rats. In the setting of reperfusion arrhythmias, a total of 1159 studies were carried out (328 in dogs, 128 in pigs, 54 in rabbits, 64 in guinea pigs, 585 in rats).

The fact that acute ischaemia affects the incidence of arrhythmias in coronary heart disease in a variety of ways makes it impossible to investigate its pathophysiology in a single experimental model. Thus, acute ischaemia occurs as one of the triggers for arrhythmias in chronic infarction [92], in hypertrophy and failure, or it may occur consequently to coronary occlusion (thrombosis or spasm) in previously relatively healthy individuals [93]. This spectrum of pre-existing alterations is likely to affect the role of acute ischaemia, since infarction, hypertrophy and failure are associated with changes in the pre-existing arrhythmogenic substrate [94,95]. Moreover, experimental-

ists distinguish between total and partial coronary occlusion, the latter being associated with so-called 'low flow' ischaemia, a pathophysiologic entity which leads to electrical and ionic changes different from the changes associated with immediate and total occlusion [96,97]. In the clinical settings, it is not always evident whether acute myocardial ischaemia is associated with or without residual flow through the occluded or collateral arteries. In the light of these complexities the discussion about the applicability of animal models of acute ischaemia to the human situation is certainly justified.

A first basic question concerns the comparison of the type and incidence of the electrical changes and arrhythmias among different species. In larger species (dog, pig, cat) the arrhythmias during acute ischaemia are relatively well characterized. Thus arrhythmias occur in two distinct phases (so-called 'phase IA' and 'phase IB', Ref. [98]). These two phases are associated with distinct changes in the electrical tissue properties. In the first phase, IA, (up to approximately 8–10 min of coronary occlusion), there is a rapid change in electrical membrane properties associated with metabolic acidification (anaerobic glycolysis), and cellular loss and extracellular accumulation of $[K^+]$ [99,100]. The impact of these changes are a rapid depolarization of the ischaemic myocytes, and a loss of amplitude and duration of the transmembrane action potential [101,102]. Moreover, there is a marked lengthening of the refractory period, which becomes sensitive to the lengths of the previous intervals of local excitation. As shown in experimental studies and explained recently in computer simulations [103,104], these changes are followed by specific changes in the excitation and conduction patterns. Thus, the decrease in conduction velocity during acute ischaemia is relatively small and conduction block, which changes its location from beat-to-beat, occurs early and abruptly [104]. The resulting ventricular tachycardia, frequently issuing into fibrillation, has a characteristic appearance [90]. It is made up by large and highly unstable re-entrant circuits (several millimetres inner circle length). The second phase of arrhythmias, IB, occurs approximately 10 to 15 min after coronary occlusion and is related to the electrical uncoupling of the myocytes [105]. Although the IB arrhythmias have not been analyzed in detail by mapping studies, it is likely that the re-entrant circuits during this phase are significantly smaller, because partial electrical uncoupling allows for much smaller conduction velocities [106], and therefore scales the circus movements to a smaller size. The studies obtained in relatively large animals (dog, pig, cat) raise two questions: (1) Are the arrhythmias occurring after acute coronary occlusion in humans comparable to those observed in the animal models? (2) Do the experimental arrhythmias differ among animal species? The first question cannot be answered directly. However, several observations provide circumstantial evidence that the electrical changes during acute ischaemia in humans and large animal hearts are similar. In an experiment carried out in an isolated perfused human heart, the extent and time course of the changes in transmembrane action potentials were almost identical to those observed in pig and dog hearts [107]. While there seems an approximate similarity among the electrophysiological changes observed in large animals and in certain cases of acute ischaemia in humans, several experimental observations indicate that the arrhythmias observed in small animals (guinea pigs, rats) during acute ischaemia differ from the arrhythmias observed in larger species. First, as mentioned above, the very early (and frequent) type IA arrhythmias require a large tissue mass for the re-entrant circuits to be maintained. The dependence of re-entry (tachycardia and fibrillation) on tissue size is an old observation, made already in 1914 by Garrey [57]. Indeed, most of the work done on ventricular fibrillation in rat hearts indicates that VF in this species occurs at a time corresponding to the IB arrhythmias, and no clear separation of IA from IB arrhythmias has been described in small animal species.

A number of further processes critical for the electrical changes in acute myocardial ischaemia might be different in rats and guinea pigs from larger species. Extracellular accumulation of $[K^+]_o$ and metabolic acidification, which are likely to be linked to each other, are the main factors determining the extent of the depolarization of the resting membrane, the changes in action potential upstroke and changes in refractoriness. In ischaemic regions devoid of collateral flow, there is a sharp transition from ischaemic to normoxic tissue with respect to local pO_2. In contrast, the acidification of the tissue, and the extracellular accumulation of $[K^+]_o$ show a gradual decrease from the centre towards the border of the ischaemic region [108,109]. In other words, although a given tissue site may be fully ischaemic, the extent of the ionic changes, which form the basis for the disturbance in electrical function, depends on the diffusion of products of the ischaemic metabolism toward the non-ischaemic border. Both K^+ and CO_2 have been invoked in this diffusion process [110,111], whereby CO_2 seems to be a particularly important factor, because it has a high diffusion coefficient and is bound in large quantities by the carbonic buffer system [112,113]. Along this line of reasoning, it has to be assumed that the process of diffusion will not only affect the gradients between the centre and the border of an ischaemic region, but it will also lead to a relatively smaller change in extra- and intracellular pH and K^+ in hearts with a small ventricular mass, and consequently affect the electrical changes of the ischaemic myocytes [111]. In a series of experiments in which extracellular potassium $[K^+]$ accumulation was compared among a variety of species, the maximal $[K^+]_o$ levels reached during acute ischaemia in rats were by approximately 20–30% lower than those observed in guinea pigs or rabbits [113,114].

Besides the macroscopic dimension of the ventricles, intrinsic differences in normoxic metabolism may also

exist among species. In rats such differences have been shown with respect to the duration and shape of the transmembrane action potential and the homeostasis of cellular Na^+ and Ca^{2+}. Thus the relatively high normal intracellular Na^+ activity in the normal rat affects the working mode of the Na/Ca exchanger and may lead to earlier Ca^{2+} overload in depolarized cells. Interestingly in rats, this difference can be reversed by inhibition of thyroid hormone production [115].

In the past years, so-called remodelling of cardiac tissue in various cardiac diseases and with a variety of stimuli has gained a wide interest. Many of these remodelling processes which occur in ischaemia, chronic infarction, myopathy, hypertrophy and failure, may change the substrate for electrical excitation and conduction at any level. Thus, the macroscopic tissue architecture may get more discontinuous via the increase in connective tissue. The expression of gap junctions can change as well, as may the expression of a large number of membrane ionic channels responsible for excitation. The results of all these studies demonstrate that assessment of pathophysiological mechanism has to consider the dynamics of events and related variables not only on short term (e.g. in the minutes following coronary occlusion) but also on middle (e.g. after preconditioning [116,117]) and on longer term (genetic remodelling [118–121]). This increasing complexity should have an impact on the selection and definition of animal models. First, in many important diseases, it is probably wrong to think that a given animal model can exactly mimic a certain disease and the 'individuality' of a certain disease pattern. In most cases they can only address partial aspects of the disease mechanism. Second, animal models used to assess arrhythmias should be designed in such a way that the most important variables methodologically followed.

The factors that determine whether, and if so, how frequently, ventricular fibrillation occurs include the size of the ischaemic area, the degree of collateral flow, heart rate, the use of anaesthetics, stress in conscious animals, the mode of coronary artery occlusion, presence of a previous infarction, activity of the autonomous nervous system, hypertrophy in the non-ischaemic myocardium [88,89]. The three most important factors are size of the ischaemic area, the degree of collateral flow and heart rate [122–127]. There is a variation among species in the degree of collateral blood flow following coronary artery occlusion [96]. For example, in rat, rabbit and pig hearts collateral flow is not significantly different from zero, in the guinea pig it is not different from normal control flow [128]. In the dog, an animal often used in studies on ischaemia-induced arrhythmias, there is a variation in pre-existing collaterals, and depending on the degree of collateral flow, the incidence of ventricular fibrillation may vary from zero to 100% after occlusion of a major coronary artery [124,126,127]. Similarly, occlusion of the left anterior descending coronary artery results in a variation of size of the ischaemic zone [122–124] and ''this can account for a substantial portion of non-drug related variability in outcome of antiarrhythmic trials using the canine coronary occlusion or release model'' [123]. This statement was corroborated by Trolese-Mongheal and colleagues [129] who collected data from various laboratories on 658 dogs in which the left anterior descending coronary artery was suddenly ligated. When control series consisted of 10 dogs, the incidence of ventricular fibrillation varied from 0 to 70%; when the control group counted 20 animals, the incidence varied from 5 to 55%, and even in series of 100 dogs, there still was a range of 14 to 36%. The papers emphasizing the importance of pre-existing collaterals were published between 1970 and 1986. A Medline search unearthed 28 studies published between 1982 and 1996 in which a major coronary artery was occluded in dogs to test the effect of antiarrhythmic drugs. The control series varied from 6 to 40 animals, and since the factors mentioned above were not controlled, interpretation of the results must be made with great caution.

3.3. The ventricular arrhythmias of myocardial infarction

A distinction has been made in arrhythmias occurring in the subacute phase of myocardial infarction (hours to days after acute obstruction of a coronary artery) and in the chronic phase (weeks to months). Almost all of the experimental work has been performed in dogs (a Medline search over the past 4.5 years identified 25 dog studies, one in the rat and one in the pig).

The spontaneous arrhythmias that occur in the dog during the subacute phase resemble those in patients recovering from an acute myocardial infarction: accelerated idioventricular rhythms or slow ventricular tachycardias that usually do not degenerate into ventricular fibrillation (for a detailed description see Refs. [88] and [89]). A great deal is known about electrophysiological changes in both Purkinje and muscle cells that survive the infarct. However, since the arrhythmias of the subacute phase are usually benign, and since the patients are still in hospital so that in case ventricular fibrillation would occur adequate resuscitation and defibrillation will be provided, the knowledge derived from experimental models has not contributed to establish therapeutic strategies during this phase of myocardial infarction.

A great deal of information about the electrophysiological characteristics of ventricular tachycardia induced by programmed electrical stimulation has been gathered in dogs with a healing infarct, and many similarities exist between these arrhythmias and those induced in patients. There are, however, several differences between the experimental and the clinical tachycardias. Thus, in dogs, ventricular tachycardias can be easily induced by premature ventricular stimulation in the first week following coronary artery occlusion, but after the first week in-

ducibility decreases [130] and sometimes the arrhythmia cannot be induced at all [131]. This is different in human patients: after five days, ventricular tachycardias can be induced in about 10% of patients [132], but in 20 to 50% after three weeks [132–134]. Moreover, in the dog, the re-entrant circuit responsible for the tachycardia is usually located in the so-called subepicardial border zone, i.e. the thin layer of surviving subepicardial myocardium overlying the infarct, whereas many of the sustained tachycardias in humans with a healed infarct originate in the subendocardial region [89]. Despite these differences, the experimental studies have provided important information about the characteristics of the re-entrant circuits and in so far studies in humans were able to study these characteristics, the similarities far outweigh the differences. There is no doubt that the experimental findings have been of crucial importance for initiating therapeutic strategies, such as mapping-guided surgery, catheter ablation, or antitachycardia pacing [135–137]. The problems arise when experimental studies are performed without electrophysiological measurements, noting only the incidence of arrhythmias. As is the case for acute ischaemia, many factors determine the incidence of ventricular tachycardia or fibrillation in a heart with a healed infarct. Both the size and the structure of the infarct determine whether or not arrhythmias occur and the characteristics of arrhythmias that do occur [138,139]. Without the presence of surviving muscle fibres in the infarcted region that provide the anatomical substrate for re-entry, arrhythmias may not occur [140–142]. The location of the surviving myocardial fibres might also determine whether the autonomic nervous system might contribute to arrhythmogenesis. Since efferent sympathetic fibres travel in the left ventricular subepicardium, a transmural infarct extending to the epicardial surface may damage them and produce nonhomogeneous sympathetic denervation of normal myocardium distal to the infarct [143], which may be arrhythmogenic [144,145]. These facts are important for the interpretation of animal experiments in which only one factor important for arrhythmogenesis is considered. The studies of Schwartz and colleagues have been instrumental in initiating clinical studies on baroreflex sensitivity as a risk factor for arrhythmias in post-infarction patients [146–148]. In essence, their experimental model is a conscious dog with a healed anterior infarct in which during exercise, an occluder on the circumflex coronary artery is occluded for two minutes. It appeared that dogs with low baroreflex slopes (susceptible dogs) developed more often ventricular fibrillation than dogs with steep baroreflex slopes (resistant dogs). These results were interpreted as indicating that strong vagal reflexes would protect an individual with an infarction against stress- and ischaemia-induced ventricular fibrillation. Indeed, clinical studies [149,150] have confirmed that baroreflex sensitivity is an important determinant for sudden death and inducibility of ventricular tachycardia in post-infarction patients. Still, both in animals and patients there is a considerable overlap in baroreflex slope in the groups with and without arrhythmias, so that in an individual case no absolute prediction can be made whether or not arrhythmias will develop. This is of course due to the fact that sudden death is not due to a single pathophysiologic event. It is in this respect noteworthy that Legato found that susceptible dogs had larger and more inhomogeneous infarcts than resistant dogs [151].

3.4. Animal models and antiarrhythmic drugs

Generally speaking, antiarrhythmic drugs exert their effects largely by modulating conduction velocity, or refractory period duration, or both. Conduction velocity depends on the one hand on the passive electrical properties of cardiac tissue, on the other hand on the characteristics of the Na^+ channels and Ca^{2+} channels. Whilst there is some evidence that, at least in the Purkinje system, conduction velocity increases in proportion to the size of the heart, most likely due to an increase in the space constant [152,153], to our knowledge very little is known about species differences in the density and kinetics of Na^+ and Ca^{2+} channels. In contrast, there are marked differences among species in the K^+ currents that largely determine repolarization, so that action potential duration and duration of the refractory period differ widely in various species. For that reason, we will concentrate on species differences in refractory period duration.

It is generally assumed that agents that prolong the action potential duration, and thereby the refractory period, are effective against re-entrant arrhythmias in two ways: by prolonging the wavelength (the product of refractory period and conduction velocity), the initiation of a re-entrant arrhythmia by a premature impulse may be prevented [154] or an existing arrhythmia may terminate because the wavelength becomes too large with respect to the re-entrant circuit, so that by closing the excitable gap, the head of the re-entrant wavefront will hit the wall of refractoriness and propagation stops 155a,b. Even though these explanations may be too simplistic because some studies have shown that re-entrant arrhythmias may be terminated by agents that prolong the refractory period without entirely closing the excitable gap [156], it is clear that the duration of the diastolic interval is an important parameter when assessing the efficacy of an anti-arrhythmic drug that prolongs refractoriness in an animal model.

Fig. 1 shows the relation between the basic cycle length and the action potential duration or effective refractory period in the ventricle (or in isolated trabeculae or isolated cells) in several species [157–161]. In contrast to *all* other species it may be appreciated that in the rat there is no shortening of refractory periods at the shorter cycle lengths. Also, there are considerable differences in refractory periods between the dog and the pig, although

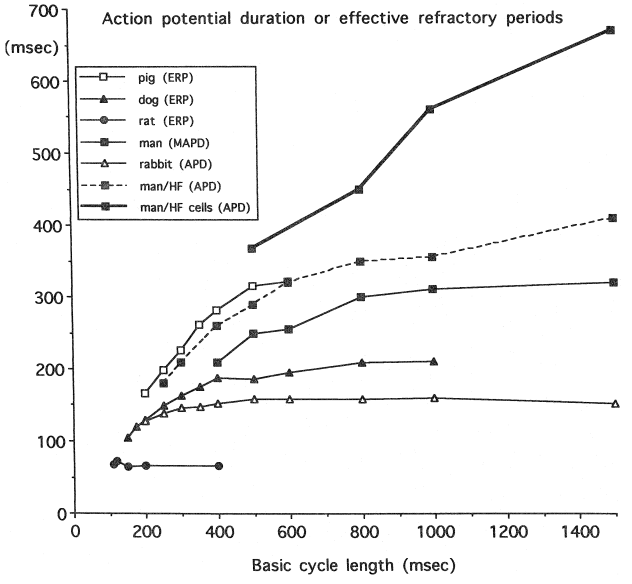

Fig. 1. Relation between (steady state) cycle length and (monophasic) action potential duration or effective refractory period in several species (see inset for details). Data have been taken as follows: pig [159], dog [157], rat [158], man [161], rabbit [160], man/HF (heart failure) [160], man/HF (heart failure isolated cells (unpublished data, Veldkamp MW). ERP: effective refractory period; APD: action potential duration; MAPD: monophasic action potential duration.

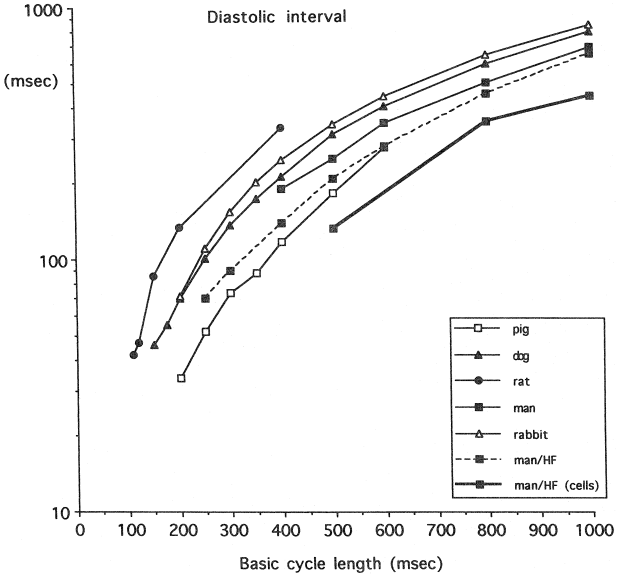

Fig. 2. Relation between (steady state) cycle length and diastolic interval (see inset for details). Data have been taken as indicated in the legend to Fig. 1.

these species have comparable cardiac dimensions and in vivo and in vitro cycle lengths. The discrepancy between the monophasic action potential duration in the normal human ventricle (Fig. 1: filled squares, solid line) and action potential duration in ventricular trabeculae from failing human hearts (Fig. 1: filled squares, dashed line) underscores the prolongation of action potential duration associated with heart failure. In the latter study [160] patients were selected who were not on amiodarone, quinidine or sotalol, thereby excluding drug effects in addition to the effect of heart failure itself. Action potential duration in single cells isolated from failing human hearts (Fig. 1: filled squares, fat line) is even further prolonged compared to trabeculae. It cannot be determined with certainty whether this follows from the cell isolation procedure, but it certainly sets limits to the choice of a *relevant animal model*. Fig. 2 shows the diastolic interval along the ordinate (log scale used for better description of the data at the more relevant shorter cycle lengths) versus the cycle length. Fig. 2 shows that rat ventricle is not the first choice if one aims at 'filling up' the diastolic interval by means of a class I or class III or an experimental anti-arrhythmic agent. On the other hand, porcine ventricular myocardium appears to have a diastolic interval similar to that in human ventricle. In line with these data it may be interesting to assess the number of studies performed in several species on the effects of anti-arrhythmic agents on action potential duration. Table 1 shows the results of a Medline search for the number of studies performed on the effects of anti-arrhythmic agents on action potential duration in different species between 1966 and 1992, and between 1993 and 1996. The rabbit is often used for electrophysiological research, probably because it constitutes a reasonable compromise in terms of cardiac dimensions, basic electrophysiological characteristics and cost. Therefore it has been chosen as the reference species for a comparison of the species chosen in this area of research in the past and in more recent years. Table 1 shows that the use of the pig and the guinea pig has increased during recent years and that the use of the rat is small compared to other species which seems justified on the basis of data in Figs. 1 and 2. Also, the use of human tissue has increased.

Table 1
Studies on action potential duration and antiarrhythmic agents

Species	1966–1992	Relative number	1993–1996	Relative number
Dog	123	1.9	21	1.2
Pig	101	1.6	48	2.8
Cat	7	0.1	6	0.4
Rabbit	64	1.0	17	1.0
Guinea pig	100	1.6	45	2.6
Rat	19	0.3	6	0.4
Man	22	0.3	22	1.3

Absolute and relative numbers of studies performed on the effect of anti-arrhythmic agents on action potential duration in several species between 1966 and 1992, and between 1993 and 1996, as included in Medline.

4. Conclusions

It is clear that species differences do exist with respect to factors that determine arrhythmogenesis and it is also clear that no animal model will accurately mimic the human patient suffering from, or threatened by an arrhythmia.

Nevertheless, the knowledge gathered from animal studies undoubtedly has been instrumental in devising diagnostic and therapeutic strategies both in supraventricular and ventricular arrhythmias. It is our conviction that in the future, new knowledge will be obtained from experiments performed at many levels: in systems expressing and testing the functions of molecules involved in electrical excitation, in single cells, cell cultures, excised cardiac preparations, isolated whole hearts, whole hearts in anaesthetized animals, and in conscious animals. It will be the combination of such investigations, rather than a single model or experimental technique, which will lead to novel strategies for diagnosis and treatment. Finally, electrophysiological studies should be encouraged in animals with 'naturally' occurring cardiovascular disease [162,163].

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